Draft Guidance for Industry and FDA Staff

Functional Indications for Implantable Cardioverter Defibrillators

DRAFT GUIDANCE

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Preface

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Functional Indications for Implantable Cardioverter Defibrillators

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Introduction

The term "functional indication" refers to an indication statement for a medical device that describes what the device does and does not specify an indicated patient population.

Many implantable cardioverter defibrillators (ICDs) currently have a functional indication. This document is designed to provide guidance regarding the intended patient population for ICDs with an approved functional indication, and cardiac resynchronization therapy defibrillators (CRT/ICDs) with an approved indication that describes the function of the ICD component; labeling, advertising, and promotion for those ICDs and CRT/ICDs; and when to submit an application for an investigational device exemption (IDE) for a study involving a potential new patient population for an ICD with an approved functional indication.
FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance documents means that something is suggested or recommended, but not required.

Background

The indication statement for ICDs has evolved in the last several years. Prior to 2000, the indication statement for most ICDs included detailed language to describe the type of patient that would benefit from an ICD, for example:

> *The ICD is indicated for use in patients who are at high risk of sudden cardiac death due to ventricular arrhythmias and who have experienced one of the following situations: Survival of at least one episode of cardiac arrest (manifested by loss of consciousness due to a ventricular tachyarrhythmia); or recurrent, poorly tolerated, sustained ventricular tachycardia.*

The indication statement sometimes included additional patient characteristics, for example:

> *…prior myocardial infarction, left ventricular ejection fraction of 35% or less, and a documented episode of nonsustained ventricular tachycardia with an inducible tachyarrhythmia.*

On June 20, 2000, FDA held a public meeting of the Circulatory System Devices Panel to introduce the concept of a functional indication and to allow public comment by interested parties, including representatives from industry. As background, FDA discussed some of the challenges presented by the indications that were currently approved at the time. Specifically, FDA asserted that:

> *These [original] indications are … the entry criteria for the studies that were used to demonstrate effectiveness and safety of the [ICDs]; and indications were presumably chosen to assure a high prevalence of life-threatening ventricular arrhythmias in the studies of the devices. The indications, as stated, give the impression that the FDA-approved labeling for these devices defines the population at risk. That was not the purpose of the studies…. The purpose of the study [sic] were to evaluate the safety and effectiveness of the devices in a high prevalent [sic] population.[1]*

In addition, FDA stated:

> *[FDA assumes] that the information on diseases or conditions that cause life-threatening ventricular arrhythmias is available to the physician from sources other than the device labeling. Examples of this are the American Heart Association, American College of Cardiology and Guidance publications, as well as reports of individual studies. [1]*

FDA presented the functional indications as a least burdensome method of allowing the clinical community to identify the patient populations that would benefit from an ICD.

The functional indication for ICDs typically reads:

> *The ICD is intended to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias.*

Both the Panel and representatives from industry endorsed the concept of a functional indication and the basic language proposed by FDA. Currently, most ICDs have a functional

indication statement with very similar language to that recommended by FDA at the panel meeting.

During the open discussion at the June 2000 Panel meeting, the Panelists identified the American College of Cardiology/American Heart Association/North American Society of Pacing and Electrophysiology[1] (ACC/AHA/NASPE) Practice Guidelines as one source for determining who would benefit from an ICD. The panel believed that acceptance by the ACC/AHA/NASPE Practice Guidelines that a particular patient population would benefit from an ICD reflected an appropriate level of concurrence across the electrophysiology clinical community. The Guidelines are based on results from the large clinical trials that were summarized at the Panel meeting and that FDA relied upon when it approved functional indications for many of these ICDs.

Per the June 2000 panel meeting discussion, FDA intended to provide guidance to industry that would explain the scope of our decision to approve ICDs with functional indications. Since that time, it has also become necessary to develop guidance in the area of advertising and promotion for ICDs that have a functional indication statement, since these aspects were not specifically addressed by the panel. The purpose of this guidance document is to set forth those recommendations.

Scope of this Document

This guidance is limited to discussion about the intended patient population for ICDs with an approved functional indication and CRT/ICDs with an approved indication that describes the function of the ICD component; labeling, advertising, and promotion for those ICDs and CRT/ICDs; and when to submit an IDE for a study involving a potential new patient population for an ICD with a functional indication. This guidance document is applicable only to ICDs with an approved functional indication and CRT/ICDs with an approved indication that describes the function of the ICD component.

Defibrillators Appropriate for ICD Functional Indications

A functional indication is appropriate for ICD technology because ICDs function interchangeably across various models and across diverse patient populations. While different model ICDs may offer different features and functions, the life-saving attributes of most ICD models are based on similar concepts of sensing, detecting, classifying, and treating ventricular arrhythmias using pacing therapy (antitachycardia pacing) and/or high-energy shocks (defibrillation). The participants at the June 2000 Panel meeting understood this. Their recommendations reflected their determination that an assessment of mortality benefits in the medical literature is the primary measure of safety and effectiveness for an ICD in a particular population and that such benefit would not be expected to hinge on the

[1] The North American Society of Pacing and Electrophysiology (NASPE) is now known as the Heart Rhythm Society (HRS).

exact model of the ICD. FDA agrees with this determination and believes that ICDs are appropriate for a functional indication when, by virtue of their similar design and characteristics, they would be expected to demonstrate the same level of safety and effectiveness as the ICDs represented in the literature summary that was reviewed at the June 2000 Panel meeting.

There are a number of devices that may be similar in design to an ICD but that FDA has not approved with a functional indication. For example, FDA currently does *not* consider certain defibrillator types appropriate for functional indications because (1) they do not function interchangeably across models and patient populations, (2) their life-saving attributes are not based on similar concepts of sensing, detecting, classifying, and treating ventricular arrhythmias, or (3) their risk-benefit profile is not appropriate for the entire ICD population. The defibrillators that FDA does not consider appropriate for functional indications include external defibrillators, wearable defibrillators, de-featured implantable defibrillators where the risk-benefit profile suggests the need for a more narrow intended patient population, or defibrillators that use radically different detection algorithms, shock waveforms, or electrode configurations than those under discussion at the June 2000 Panel meeting.

Any PMA submission in which a manufacturer seeks a functional indication statement for its ICD should include data demonstrating that the particular ICD has the ability to sense, detect, classify, and treat life-threatening ventricular arrhythmias using antitachycardia pacing and defibrillation, and that the ICD has a favorable risk-benefit profile.

Indicated Patient Population

Although FDA expects all ICDs with functional indications to function similarly in all patients, this does not mean that the risk-benefit profile is the same across all patient populations. What varies from patient group to patient group is the overall need for defibrillation, based on that particular patient population's incidence of life-threatening ventricular arrhythmias.

FDA considers a particular patient population to be indicated for an ICD if clinical data are available to demonstrate (1) that the population is at risk for developing life-threatening ventricular arrhythmias and (2) that ICD use in that population results in a significant mortality benefit. If such data is not available for a patient population, new mortality trials should determine whether these patients are indicated for an ICD by demonstrating that the risk-benefit profile for the new patient population is favorable.

Several manufacturers produce ICDs that also deliver CRT. These "CRT/ICD" devices may have an indication statement that specifies an indicated heart failure patient population based on the CRT component of the device but describes the function of the ICD component. CRT does not have a functional indication. Therefore, FDA believes a particular patient population is indicated for a CRT/ICD if the population meets the heart failure criteria based on the CRT component as specified in the indication statement and if clinical data are

available to demonstrate (1) that the population is at risk for developing life-threatening ventricular arrhythmias and (2) that ICD use in that population results in a significant mortality benefit.

ICD Labeling

The functional indication does not alter the basic requirements for device labeling, including information for use (see 21 CFR Part 801, 801.109(c)). To meet such requirements, labeling should include a description of the device as well as a summary of the clinical and non-clinical studies that support the safety and effectiveness of that manufacturer's ICD. The device description should be comprehensive and include, among other specifications, those typically characterizing ICD performance such as the sensitivity and specificity of the detection algorithm(s). As discussed below, if a manufacturer wishes to modify its device labeling to describe the benefit from an ICD in a particular population, the sponsor should submit a PMA supplement with data characterizing that benefit.

Promotion and Advertising

This section will discuss promotional statements with regard to the intended patient population, device performance, and patient outcomes for ICDs and CRT/ICDs.

1. Promotional statements about the intended patient population for ICDs.
As discussed above, a patient population is considered to be indicated for an ICD if publicly available clinical data demonstrate (1) that the population is at risk for developing life-threatening ventricular arrhythmias and (2) that ICD use in that population results in a significant mortality benefit. If a manufacturer were to claim that its ICDs are indicated for a patient population without such evidence, FDA would view these claims as potentially false and misleading.

2. Promotional claims about ICD performance and patient outcomes.
The ICD functional indication statement, by definition, describes the function of the device and does not explicitly specify expected patient outcomes. An ICD with a functional indication may be promoted for its primary use, as described by the approved indication, which is for the treatment of life-threatening ventricular tachyarrhythmias. This implies a mortality benefit derived from having these arrhythmias successfully treated. Therefore, it may be reasonable for a manufacturer to make claims regarding a mortality benefit for its ICD with a functional indication in a particular population if those claims are based on clinical data, as described above.

Other promotional statements, such as, reduction in hospitalizations, or symptom relief of other concomitant conditions, are not described by the currently approved ICD functional indication. Before promoting an ICD for a new indication, the manufacturer must submit to

FDA a PMA supplement seeking a change in that ICD's indication and labeling (21 CFR 814.39(a)).

3. *Promotional statements about CRT/ICD indications, performance, and patient outcomes.* As discussed above, CRT does not have a functional indication. A manufacturer may promote its CRT/ICD device as indicated for a particular population if the population meets the heart failure criteria based on the CRT component of that manufacturer's CRT/ICD as specified in the approved indication statement for that particular device and if clinical data demonstrate (1) that the population is at risk for developing life-threatening ventricular arrhythmias and (2) that ICD use in that population results in a significant mortality benefit.

All promotional statements for a CRT/ICD device, including any mortality benefit not directly attributed to the ICD component of the device, should be supported by the approved indication and labeling for that manufacturer's device.

When to Submit an IDE

FDA recommends that an IDE be submitted for any study that is intended to evaluate the safety and effectiveness of ICD therapy in a new patient population. A population is considered to be new if it is not currently indicated for an ICD due to the fact that clinical data are unavailable to demonstrate (1) that the population has an increased risk for developing life-threatening ventricular arrhythmias and (2) that ICD use in that population results in a significant mortality benefit.

When to Submit a PMA/Supplement

A manufacturer must submit a PMA supplement for its ICD with a functional indication whenever it seeks to make a change affecting the safety and effectiveness of the device, with the exception of certain manufacturing changes (21 CFR 814.39). This requirement applies to labeling changes that affect the safety and effectiveness of the device (21 CFR 814.39(a)(2)). As a result, manufacturers generally must submit a PMA supplement when they wish to modify device labeling. As discussed above, a manufacturer may make a specific claim about its ICD other than a mortality benefit if it has received approval for a PMA or PMA supplement that includes labeling to support the claim.

References

[1] Transcript of the Circulatory System Devices Panel meeting, June 20, 2000; http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3628t2.rtf